Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 61, 63-90, 92-120 are pending in the application, with claims 61 and 90 being the independent claims. Claims 62 and 91 are sought to be canceled without prejudice or disclaimer. Support for these amendments can be found, *inter alia*, on page 1, lines 10-26; page 3, lines 18-31; page 4, line 10 to page 6, line17; and in the Examples. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 102(e)

For rejections under 35 U.S.C. § 102, the Federal Circuit held "[a] claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California,* 814 F.2d 628, 613, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

Vande Woude *et al.*

Claims 61-64, 66-70, 77-83, 87-93, 95-99, 106-112, 116-120 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Vande Woude *et al.* (U.S. Pat. No.

5,645,988). The Examiner alleged that Vande Woude *et al.* teaches a parallel screening method for determining the pharmacological effects of an anti-cancer drug on the activity of either different biological target molecules contained in cancer cells of the same type or the same biological target molecule in different cell types, the method comprising the steps of the instant claims. Applicants respectfully traverse this rejection as it may apply to the amended claims.

The instant claims are directed to high throughput parallel screening methods in which a test substance is applied in one operation to more than one cellular substrate, then measuring the effect of the test substance on the activities of different biological target molecules using different assays or assay formats for each substrate. This high throughput method is not merely a simple parallel or comparative screen, but also done in one operational step.

As discussed in the Reply filed October 28, 2004, Vande Woude *et al.* does not describe the single operation high throughput parallel screening method of the instant claims. Solely to make explicit that which was implicit, the pending claims have been amended to recite a method in which a test substance is applied in one operation to more than one cellular substrate and then the effect of the test substance on the biological activities of the cellular substrates are measured using different assays or assay formats for each substrate. In contrast, the assay of Vande Woude *et al.* makes no mention of a parallel screen that is a one step operation and only very generally describes an assay to correlate drug activity with the presence or absence of a particular DNA sequence in the cell. *See, e.g.,* columns 5, 11, 12 and the Examples. This description as well as the specific passages pointed to by the Examiner fail to teach a combination of multiple

assays into one step for a high throughput parallel screen. There is nothing in Vande Woude *et al.* to support the conclusion that a high throughput parallel screen in one operation was a feature of that assay. Because Vande Woude *et al.* does not teach each and every limitation of the rejected claims, it cannot anticipate the claims. Applicants respectfully request that the rejection be withdrawn.

Tang *et al.*

The Examiner rejected claims 61, 62, 67-73, 77-79, 90, 91, 96-102, 106-108 under 35 U.S.C. § 102(e) as allegedly being anticipated by Tang *et al.* (U.S. Pat. No. 5,710,173). Specifically, the Examiner alleged that "Tang *et al.* teach a parallel screening method (96-well microtiter plates) of claims 61-62, 90-91, of determining the pharmacological effect of a substance (anti-cancer drug) on the activity of different biological target molecules contained in test cells of same type . . ." Page 5 of the Office Action. Applicants respectfully traverse this rejection as it may apply to the amended claims.

Tang *et al.* does not describe the single operation high throughput parallel screening method of the claimed invention, which is explained in detail *supra*. The Examiner points to the 96 well format of the endpoint ELISA assay described in the Group II ELISA Type Assay Examples beginning in column 18 of Tang *et al.* as support for a parallel screen. However, there is no mention whatsoever of performing sets of different assays in parallel, much less also in one operation. As discussed in the Reply filed October 28, 2004 and reiterated herein, Tang *et al.* suggests they are performed sequentially.

> Compounds of varying degree of selectivity are useful for diagnosing the role of a receptor tyrosine kinase. For example, compounds which inhibit more than one type of receptor tyrosine kinase can be used as an initial test compound to determine if one of several receptor tyrosine kinases drive the disorder. More selective compounds can then be used to further eliminate the possible role of different receptor tyrosine kinases in driving the disorder.

Column 11, lines 4-11. The Examples describe each assay individually and do not make any reference to combining the assays in parallel into one operation. Mere use of the well-known 96 well ELISA format is not sufficient for describing a high throughput parallel screening assay according to the claimed invention. The 96 well format is typically used for the processing of multiple samples of the *same* ELISA assay, and nothing in Tang *et al.* teaches otherwise. Indeed, it appears that the multiple samples come from the same cells that are treated with different drugs as a part of a serial screen. There is no description of performing different assays or assay formats within a single operation. Performing the same assay multiple times is not a high throughput parallel screen utilizing more than one cellular substrate and different assays or assay formats in one operation. Because Tang *et al.* does not describe a single operation, high throughput parallel screening method, it does not teach each and every element of the instant claims. Therefore, Tang *et al.* cannot anticipate the claimed invention, and Applicants respectfully request that the rejection in its entirety be withdrawn.

The Examiner also rejected claim 90 and dependents thereof over the assay described in Tang *et al.* In addition to the arguments presented *supra*, Applicants point

out that claim 90 and its dependents are drawn to a single operation, high throughput parallel screening assay utilizing *different cell types* containing the *same target molecule.* The Examiner points to column 10, lines 4-29 of Tang *et al.* as support for a parallel screening assay utilizing different cell types containing the same target molecule, but Applicants respectfully traverse this characterization. This passage discloses that different tumor types have a particular oncogene, but never suggests that these different cell types may be utilized in a one operation, high throughput parallel screen as presently claimed. Tang *et al.* lacks any disclosure that different cell types may be used in the same screen. Therefore, Applicants respectfully request that for this reason, in addition to those described *supra*, the rejection of claims 90-91, 96-102 and 106-108 over Tang *et al.* be withdrawn.

Rejections under 35 U.S.C. § 103

In re Vaeck (947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)), outlines the factors required for establishing a prima facie case for obviousness: prior art references that teach all claim limitations, a motivation to combine the teachings in the references themselves or knowledge known to a person of skill in the art at the time the invention was made, and a reasonable expectation of success from the combination of elements in the references. As discussed below, Applicants respectfully assert that these requirements have not been met to support a *prima facie* argument for obviousness for the instant claims.

Vande Woude *et al.* in view of Czernilofsky *et al.*

Claims 74-76, 84, 85, 103-105, 113, and 114 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Vande Woude *et al.* in view of Czernilofsky *et al.* (U.S. Pat. No. 5,854,004). Specifically, the Examiner alleges that the claims are obvious over the parallel screen allegedly disclosed in Vande Woude *et al.* and the additional target molecules and detection systems allegedly disclosed in Czernilofsky *et al.* Applicants respectfully traverse this rejection.

As discussed *supra*, Vande Woude *et al.* does not teach the high throughput parallel screen of the instant claims. As discussed Applicants' previous Reply, Czernilofsky *et al.* does not remedy this deficiency. In column 6, lines 30-35, Czernilofsky *et al.* states that the method serves to screen substances that modulate a phospholipase C signal transduction pathway depending on an individual receptor using "sensor DNA," which is regulatory elements linked to a reporter gene, not the receptor gene itself. The screening method of Czernilofsky *et al.* is used to identify a test substance with the ability to modulate, in one type of cell, a signal transduction pathway of interest which is dependent on a specific receptor molecule of interest by providing regulatory elements responsive to that receptor or the signaling pathway to which it is connected.

When mentioning, in column 7, lines 62-67, that parallel tests may be carried out, Czernilofsky *et al.* does not refer to a single operation, high throughput parallel screening method as presently claimed. The use of cells that contain a sensor DNA responding to a different signaling pathway and that may (CRE-test cells) or may not (CRE-pretest cells) contain the receptor of interest in parallel to the actual test cells merely serves the

purpose of specificity control with regard to the predetermined signal transduction pathway of interest.

In order to make sure that the compound's modulating effect is specific with regard to the receptor, further control tests may be carried out by using cells that contain other different receptors (column 13, lines 66-68). The very use of the term "further" points out that these tests are not conducted in parallel or in one operation, but may be carried out sequentially, *i.e.* after a compound has already been identified. Such tests do not aim at identifying compounds that act on different receptors (targets). On the contrary, they have the purpose, by serving as controls, to exclude compounds that are not specific for the receptor of interest in that they also influence one or more other receptors.

There is no motivation to combine the sophisticated receptor-mediated assay of Czernilofsky *et al.* with the simple proliferation assay based on the effect of oncogenes and tumor suppressor genes of Vande Woude *et al.* Vande Woude *et al.* is in the field of cancer and oncogenes, while Czernilofsky *et al.* is directed to receptor-mediated intracellular signaling. Neither reference suggest the desirability of their assay for the other field.

Further, there would be no expectation of success without impermissible hindsight as Vande Woude *et al.* does not describe the regulatory elements of the genes assayed therein that would be required for the "sensor" DNA of the assay of Czernilofsky *et al.* Without these regulatory elements, it is impossible to adapt the signaling responsiveness of Czernilofsky *et al.* to the oncogene screen of Vande Woude *et al.* The Examiner correctly states that these regulatory elements are not claimed in the instant

application, but Applicants assert these regulatory elements would be necessary to combine the assays of Czernilofsky *et al.* and Vande Woude *et al.* since the assay of Czernilofsky *et al.* depends entirely on these elements. These elements are typically upstream from the gene under their control, and thus is not part of the gene itself, as disclosed in Vande Woude *et al.* Thus, the genes of Vande Woude *et al.* cannot be successfully combined with the sensor DNA constructs of Czernilofsky *et al.* without further information on the regulatory elements of the genes.

Further, even if such a combination were made, the limitations of the present claims would not be disclosed. Therefore, because the combination of references does not teach each and every element of the claims, contain any suggestion to combine, or have any expectation of success without impermissible hindsight, Applicants assert that the Examiner has not met the burden for a *prima facie* case for obviousness. Applicants respectfully request that the rejection be withdrawn.

Vande Woude *et al.* in view of Czernilofsky *et al.* in further view of Chalfie *et al.*

Claims 86 and 115 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Vande Woude *et al.* in view of Czernilofsky *et al.* in further view of Chalfie *et al.* Specifically, the Examiner asserted that the alleged parallel screen of Vande Woude *et al.*, the reporter genes and target receptors of Czernilofsky *et al.*, and the green fluorescent protein (GFP) of Chalfie *et al.* render the instant claims obvious. Applicants respectfully traverse this rejection.

Vande Woude *et al.* and Czernilofsky *et al.* have been discussed *supra*. As discussed in Applicants' previous Reply, Chalfie *et al.* does not remedy their deficiencies

as it merely teaches the use of GFP as a reporter gene. It does not teach the high throughput parallel screen of the instant claims or remedy any of the specific deficiencies discussed of Vande Woude *et al.* or Czernilofsky *et al.* Therefore, since this combination of references does not teach each and every element of the claims, contain any suggestion to combine, or have any expectation of success without impermissible hindsight, Applicants assert that the Examiner has not met the burden for a *prima facie* case for obviousness. Applicants respectfully request that the rejection be withdrawn.

Vande Woude *et al.* in view of Reed *et al.*

Claims 65 and 94 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Vande Woude *et al.* in view of Reed *et al.* Specifically, the Examiner asserted that the alleged parallel screen of Vande Woude *et al.* combined with the BAP and Bcl-2-related solid-phase protein binding assays of Reed *et al.* Applicants respectfully traverse this rejection.

Vande Woude *et al.* does not describe the single operation high throughput parallel screen of the instant claims, as described *supra*. As discussed in Applicants' previous Reply, Reed *et al.* does not remedy this deficiency as the screen described therein is a binding assay of proteins fixed to a solid support (*see* Figure 7 and Example VII). It does not describe the one operation, high throughput parallel screen utilizing more than one cellular substrate. The assay of Reed *et al.* only measures binding affinities of the test substances to certain proteins and cannot measure the biological effects of the test substances. Therefore, since the combination of Vande Woude *et al.* and Reed *et al.* does not teach each and every element of the claims, contain any

suggestion to combine, or have any expectation of success without impermissible hindsight, Applicants assert that the Examiner has not met the burden for a *prima facie* case for obviousness. Applicants respectfully request that the rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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